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Effect of a Single Dose of Pimobendan on Right Ventricular and Atrial Function in 11 Healthy Cats

Inaugural Thesis

to obtain the title of Doctor from the
Vetsuisse Faculty University of Zurich

submitted by

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2020

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Vetsuisse Faculty University of Zurich (2020)

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Summary (English)

The objective of this study was to investigate the effect of pimobendane on echocardiographic parameters of right ventricular and atrial function in healthy cats.

Eleven privately-owned, healthy adult cats were enrolled. Each cat underwent four echocardiographic examinations. The first and second examinations were performed one hour apart on Day 0. A third examination was done on day 1 followed by pimobendane (1.25 mg/cat) administration and a fourth examination one hour later. Parameters of right ventricular and atrial morphology and function were collected and compared among time points.

No differences were found among echocardiographic variables in the three examinations before pimobendane was administered. The fourth examination showed that several parameters were affected by pimobendane administration. Specifically, right ventricular fractional shortening and peak velocity of systolic lateral tricuspid annular motion increased ($P = 0.04$, and $P = 0.01$, respectively), whereas right ventricular end-systolic internal diameter and right atrial minimal internal diameter decreased ($P = 0.03$, and $P = 0.04$, respectively). Right ventricular fractional area change, and tricuspid annular plane systolic excursion did not change.

This novel study showed that pimobendane had positive effects on right ventricular and atrial function in healthy cats. Further studies are needed to determine whether pimobendane has similar effects in cats with cardiac diseases.

Keywords: echocardiography, systolic function, calcium sensitizer, phosphodiesterase inhibitor

Vetsuisse-Fakultät Universität Zürich (2020)

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Effect of a Single Dose of Pimobendan on Right Ventricular and Atrial Function in 11 Healthy Cats

Zusammenfassung (Deutsch)

Das Ziel dieser Studie war, den Effekt von Pimobendan auf echokardiographische Funktionsparameter von rechtem Ventrikel und Vorhof zu untersuchen.

Dazu wurden elf gesunde Katzen von privaten Besitzern in die Studie eingeschlossen. Jede Katze wurde am Tag 0 zweimal im Abstand von einer Stunde echokardiographisch untersucht. Am Folgetag wurde eine weitere Untersuchung durchgeführt, nach der jede Katze eine Dosis Pimobendan (1.25 mg/Katze) erhielt. Eine Stunde danach wurde eine weitere Echokardiographie durchgeführt. Die erhobenen Parameter der rechts ventrikulären und atrialen Funktion wurden zwischen den vier Zeitpunkten verglichen.

Es fanden sich keine Unterschiede zwischen echokardiographischen Variablen vor der Pimobendan-Gabe. Es fanden sich mehrere Veränderungen nach Pimobendan-Gabe. Die Herzfrequenz, die *right ventricular fractional shortening* und die *peak velocity of systolic lateral tricuspid annular motion* waren signifikant höher ($P = 0.02$, $P = 0.04$ und $P = 0.01$). Der rechtsventrikuläre end-diastolische Diameter und der rechts atriale minimale innere Diameter sanken signifikant ($P = 0.03$ und $P = 0.04$). Die rechtsventrikuläre *fractional area change* und die *tricuspid annular plane systolic excursion* wurden nicht verändert.

Diese Studie zeigt einen positiven Effekt von Pimobendan auf die rechtventrikuläre und atriale Funktion bei gesunden Katzen auf. Weitere Studien sind gefragt, um zu zeigen, ob dieser Effekt auch bei Katzen mit Herzerkrankungen nachgewiesen werden kann.

Stichworte: Echokardiographie, systolische Funktion, Kalzium-Sensitizer, Phosphodiesterase-Hemmer

Publication Manuscript

EFFECT OF A SINGLE DOSE OF PIMOBENDAN ON RIGHT VENTRICULAR AND ATRIAL FUNCTION IN 11 HEALTHY CATS

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Keywords: echocardiography, systolic function, calcium sensitizer, phosphodiesterase inhibitor

Abstract

Objectives - The objective of this study was to investigate the effect of pimobendan on echocardiographic parameters of right ventricular and atrial function in healthy cats.

Materials and Methods - Eleven privately-owned, healthy adult cats were enrolled. Each cat underwent four echocardiographic examinations: the first and second examinations were performed one hour apart on Day 0, and the third and fourth examinations were done on Day 1. Right after the third echocardiographic examination, each cat received a single oral dose of pimobendan (1.25 mg/cat), and the fourth echocardiographic examination was carried out one hour later. Parameters of right ventricular and atrial morphology and function were collected and compared among time points.

Results - No differences were found among echocardiographic variables in the three examinations before pimobendan was administered. The fourth examination showed that several parameters were affected by pimobendan administration. Specifically, heart rate, right ventricular fractional shortening and peak velocity of systolic lateral tricuspid annular motion increased ($P = 0.02$, $P = 0.04$, and $P = 0.01$, respectively), whereas right ventricular end-systolic internal diameter and right atrial minimal internal diameter decreased ($P = 0.03$, and $P = 0.04$, respectively). Right ventricular fractional area change and tricuspid annular plane systolic excursion did not change.

Conclusion and relevance - This novel study showed that pimobendan had positive effects on right ventricular and atrial function in healthy cats. Further studies are needed to determine whether pimobendan has similar effects in cats with cardiac diseases.

Introduction

Pimobendan is a phosphodiesterase III inhibitor and a calcium sensitizer. It is classified as an inodilator because of its two main effects, myocardial positive inotropy and arterial and venous vasodilation.[1–5] In people and dogs, the positive inotropic effect of pimobendan is not associated with an increase in myocardial oxygen consumption,[6-8] and in canine models of heart failure, this drug has been shown to have a positive lusitropic effect.[6] Pimobendan has been well studied in dogs and is part of the standard treatment of dilated cardiomyopathy and myxomatous mitral valve disease.[9–12] Interest in this cardiovascular drug as a possible treatment of subclinical and clinically overt cardiomyopathies in cats has recently emerged. Two retrospective studies reported that cats with non-taurine responsive dilated cardiomyopathy[13] and hypertrophic cardiomyopathy (HCM)[14] had prolonged survival times when pimobendan was part of their treatment protocol. The use of pimobendan also appeared to be beneficial as an adjunctive therapy for congestive heart failure in cats with heart disease of various etiologies.[15]

To date, studies investigating the effects of pimobendan on echocardiographic variables in cats have focused on the left side of the heart.[16–20] However, diseases such as arrhythmogenic cardiomyopathy, HCM or pulmonary hypertension, which involve the right ventricle (RV) or affect RV myocardial function and lead to right-sided congestive heart failure, are well recognized in cats.[21–25] It would therefore be important to determine whether an inodilator could improve RV systolic and diastolic function. To the authors' knowledge, there is only one study that evaluated the effect of pimobendan on RV function in cats; it determined that pimobendan had no effect on tricuspid annular plane systolic excursion (TAPSE) in cats with HCM.[19]

Therefore, the aim of the present study was to evaluate the effect of pimobendan on right-sided cardiac function in clinically healthy cats. We hypothesized that pimobendan has a positive effect on echocardiographic variables of RV and right atrial (RA) function.

Materials and methods

Animals

The cats enrolled in this study had also been used for a previous study that focused on left atrial function.[20] Owners of the cats signed an informed consent form, and the study was approved by the local ethical committee (protocol ID 873).

Cats were enrolled in the study provided that they were one year of age or older, clinically healthy without evidence of cardiac disease or systemic illness, stress tolerant and not aggressive, had not received any medication in the previous year and had normal systolic blood pressure (<160 mmHg).[26] Each cat underwent a complete physical examination, cardiac auscultation, systemic arterial blood pressure measurement using an oscillometric device (Vet25; SunTech), according to recommended guidelines,[26] and an echocardiographic examination. Minimal blood work was carried out to exclude azotaemia and anaemia, and serum thyroxin levels were measured in cats over 6 years of age to exclude hyperthyroidism. The cats were not sedated for this study.

Study design

Four echocardiographic examinations were carried out in each cat. On day 0, a complete echocardiographic examination was done at time 0 (D0T0) and repeated one hour later (D0T1). On the following day, each cat underwent a third echocardiographic examination (D1T0). Cats were then given a single dose of 1.25 mg pimobendan (Vetmedin 1.25 mg chewable tablet, Boehringer Ingelheim) administered orally, and a final echocardiographic examination was carried out one hour later (D1T1). The timing of the final echocardiographic examination was based on a pharmacokinetics study of pimobendan.[27] The results of echocardiography were considered normal when subjective evaluation of all four cardiac chambers by the operator (MBT) revealed a normal volume and wall thickness, and when quantitative assessment yielded an end-diastolic LV wall thickness of <5.5 mm.[28]

Echocardiography

All echocardiographic examinations were done by a single board-certified cardiologist (MBT) using a single ultrasound system (iE33 ultrasound system; Philips Healthcare) with a phased-array probe (S12-4) and continuous ECG monitoring. Cats were unsedated and gently placed in right or left lateral recumbency to obtain the appropriate echocardiographic views.[29] The morphological and functional echocardiographic variables of the right atrium and ventricle were obtained as follows. Right ventricular end-diastolic wall thickness, RV end-diastolic internal diameter (RVIDd) and RV end-systolic internal diameter (RVIDs) were measured using a leading-edge-to-leading-edge technique from M-Mode images obtained from a right parasternal short axis view at the level of the papillary muscles. Right ventricular fractional shortening (RV FS) expressed as a percentage was calculated

using the formula: [(RVIDd – RVIDs) / RVIDd] x 100. Right ventricular end-diastolic (RVAd) and end-systolic (RVAs) areas were obtained from a left apical 4-chamber view optimized for the RV[24] by tracing the internal border of the RV (Figure 1a). Right ventricular fractional area change (RV FAC) was calculated using the following formula and expressed as a percentage: [(RVAd – RVAs) / RVAd] x 100. Longitudinal systolic function was assessed by TAPSE recorded from a left apical 4-chamber view optimized for the RV from an M-mode image measuring the maximal metric difference of the lateral tricuspid annular plane with the cursor as parallel as possible to the RV free wall (Figure 1b). Peak velocity of systolic lateral tricuspid annular motion (TV S´) by pulsed wave Doppler was obtained from a left apical 4-chambers view optimized for the RV with a sample volume size of 2 mm (Figure 1c). Attention was paid to maintaining the position of the cursor as parallel as possible to the RV free wall.

Right atrial maximum (RA_{max}) and minimum (RA_{min}) internal diameters were measured from an M-mode image obtained from the right parasternal long axis view optimized for the atria by using a leading-edge-to-leading-edge technique (Figure 1d). Right atrial fractional shortening (RA FS) expressed as a percentage was calculated using the formula: [(RA_{max} - RA_{min}) / RA_{max}] x 100. Heart rate (HR) was calculated by measuring the aortic flow time interval from a left apical 5-chamber view using a pulsed-wave Doppler trace.

All echocardiographic studies were stored off-line, and measurements were made by the same cardiologist (MBT) at the end of the study on anonymized and randomized images/loops to prevent information bias. A person not involved in the measurements carried out anonymization and randomization, and for the latter a computer-based

software was used. For each parameter, a mean of three measurements was obtained on three consecutive cardiac cycles on the same frame/loop.

Statistical analysis

Data were tested for normality by visual examination of the plots and additionally using the Shapiro-Wilks test. Normal data are presented as mean ± standard deviation while non-normal data are presented as median and interquartile range. Normally distributed echocardiographic variables were compared between different time points using one-way repeated-measures ANOVA. Post-hoc pairwise comparisons among different times were done using Tukey's multiple comparison test. Differences between non-normal variables were analysed using a repeated-measures Friedman test followed by Dunn's test. We evaluated within-day and between-day intra-observer variability with the echocardiographic values collected during the first three time points by calculating the respective coefficients of variation (CV). The percentage change for each variable after pimobendan administration was calculated and the number of cats whose percentage change exceeded the corresponding within-day CV was reported for each variable. Data analysis was done using a commercially available software program (Prism5, GraphPad Software Inc.). A value of $P < 0.05$ was considered significant.

Results

Animals

Eleven cats fulfilling the inclusion criteria were enrolled. Nine were domestic shorthair and two were British Shorthair cats. Six cats were castrated males and five were

spayed females. The age was 5.6 ± 3.5 years, and the body weight was 4.8 ± 1.0 kg. Systolic arterial blood pressure was normal in all cats (138 ± 14 mmHg). The mean pimobendan dose administered was 0.27 ± 0.05 mg/kg.

Echocardiographic variables

No differences in echocardiographic variables were recorded among the first three examinations. Pimobendan administration led to significant changes in several variables (at D1T1) compared with baseline on the same day (D1T0). Specifically, HR, RV FS and TV S´ increased ($P = 0.02$, $P = 0.04$, and $P = 0.01$, respectively), while RVIDs and RA_{min} decreased ($P = 0.03$, and $P = 0.04$, respectively) (Figure 2). All echocardiographic results are presented in detail in Table 1. Within-day and between-day CVs are reported in Table 2. The mean percentage change for HR, RVIDs, RV FS, RA_{min}, RA FS and TV S´ after pimobendan administration exceeded the corresponding within-day CV.

Discussion

Our study provides novel information on the effect of pimobendan on RV and RA function in healthy cats. Oral administration of pimobendan was associated with an increase in RV function as evidenced by the results of several echocardiographic RV variables. The decrease in RA_{min} implied an increase in RA function as well.

Not all variables of RV function were affected; TV S´ and RV FS increased after pimobendan administration, whereas RV FAC and TAPSE did not. Tricuspid annular plane systolic excursion and TV S´ are both measures of RV longitudinal function, which comprises the majority of global RV function in dogs and humans.[30,31] The lack of increase in TAPSE in our study suggests a low sensitivity for this variable with

respect to changes in RV function compared with TV S´. This finding was in agreement with a study in human patients with advanced heart failure, in which levosimendan infusion produced an increase in TV S´ with no significant increase in TAPSE.[32] Other studies in human medicine showed that RV S´ was better correlated with cardiac MRI-derived ejection fraction than with TAPSE.[33,34]

In our study, RV FS increased after pimobendan administration indicating increased RV radial function. Right ventricular FS has been used in veterinary[24] and human[35] medicine to assess RV systolic function. However, this variable is not well standardized for cats and in people it provides limited insight into global RV function.[35] Furthermore, the intra-observer variability of this variable was poor in the present study.

Interestingly, RV FAC, which represents both longitudinal and radial systolic RV function, did not change following pimobendan administration. Right ventricular FAC has been shown to be highly sensitive for RV dysfunction in humans.[34] However, in our study, we found it not easy to obtain due to the small dimension of the heart and the difficulty in adequately visualize RV blood-tissue interface. Indeed, compared with the left ventricle, tracing the internal border of the RV is generally more difficult because of endocardial trabeculation, anatomical features and echocardiographic views.[36,37] Intra-observer variability was poor for RVAs, which are used to calculate the RF FAC. In fact, RVAs had the highest CV making any parameter derived from these measurements of questionable diagnostic value.

Heart rate increased after pimobendan administration compared with all prior time points. This may have been due to a positive chronotropic effect of pimobendan, which has been observed in ex-vivo studies on cardiomyocyte preparations from dogs and guinea-pigs.[2,38] Compensatory mechanisms secondary to arterial

vasodilation (reduced afterload) may be another reason. An increase in HR can increase myocardial cell contractility (Bowditch effect) leading to increased systolic function.[39] This effect may have positively influenced RV function in our study. A reduction in afterload attributable to pimobendan may also have contributed to changes in RV functional parameters, in addition to the direct inotropic effect of this drug on cardiomyocytes.[36,40,41]

Improved RV function after a single dose of pimobendan was reported in 80 healthy dogs, based on increased TAPSE, RV FAC and RV S´ compared with pretreatment values.[42] In human patients with pulmonary hypertension, TV S´ increased in the group receiving levosimendan infusion but not in the placebo group.[32] When all results including ours are considered, they suggest that this inodilator has a positive effect on RV systolic function and TV S´ is a sensitive parameter for documenting the effect.

Right atrial minimal internal diameter was reduced after pimobendan administration, but RA FS was not significantly increased, even though its mean percentage change after pimobendan administration was higher than the mean within-day CV. Lack of significance may be due to the small number of cats and the poor intra-observer variability of the measurement. Nevertheless, the reduction in RA_{min} also suggests a positive inotropic effect on RA cells. A direct effect has been shown in an ex-vivo study of human RA myocytes and in murine cells from the left atrium.[44]

In addition, RA functional parameters are strongly dependent on loading conditions, which one would expect to be altered by pimobendan (namely, reduced preload and increased RV lusitropy).[43] Similar to changes in the right ventricle, alterations in HR affecting RA preload and the associated Bowditch effect may have influenced our evaluation of RA function. Lastly, we measured RA diameters in M-mode on a right

parasternal long axis view. This variable is also affected by translational motion of the heart base toward the apex during RV contraction, which therefore can affect measurements.

The primary limitation of this study was the small sample size. It is possible that the study was underpowered to find significant differences for some echocardiographic RV functional parameters, especially those that may have had limited sensitivity. Another limitation was that only healthy cats were studied. The effect of a drug on healthy cardiomyocytes may not be reproducible in cats with diseases involving cardiomyocytes.

Conclusion

Our results suggest that pimobendan has a positive effect on RV and RA function in healthy cats. Further studies are warranted to determine whether pimobendan can be used to treat right-sided cardiac disease in cats.

Acknowledgments

We would like to thank the owners of the cats for allowing their animals to participate in the study.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and publication of this article: This work was supported by the “Tieraerztliche Verrechnungsstelle GST AG”, CH-9016 St. Gallen, chair Kaspar Rohner.

Ethical Approval and Informed Consent

This work involved the use of non-experimental animals (owned or unowned) and procedures that differed from established internationally recognised high standards (‘best practice’) of veterinary clinical care *for the individual patient*. The study therefore had ethical approval from an established committee as stated in the manuscript.

Informed Consent

Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken (either prospective or retrospective studies).

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Legends to figures

Fig. 1 Selected echocardiographic variables of right ventricular and atrial function in a healthy cat. (a) Right ventricular end-diastolic (left) and end-systolic (right) areas obtained from a left apical 4-chamber view optimized for the right ventricle measured by tracing the internal border of the right ventricle. (b) Tricuspid annular plane systolic excursion obtained from a left apical 4-chamber view optimized for the right ventricle from an M-mode image measuring the maximum metric difference of the lateral tricuspid annular plane (dotted lines) with the cursor as parallel as possible to the right ventricular free wall. (c) Peak velocity of systolic lateral tricuspid annular motion (dotted line) obtained from a left apical 4-chamber view optimized for the right ventricle using pulsed wave tissue Doppler imaging. (d) Right atrial maximum and minimum internal diameters measured on an M-mode image obtained from a right parasternal long axis view optimized for the atria using a leading-edge-to-leading-edge technique

Figure 2 Echocardiographic variables that changed from D1T0 to D1T1 (one hour after pimobendan administration) in a group of 11 healthy cats. HR = heart rate, RA min = right atrial minimum internal diameter, RVIDs = right ventricular internal diameter in systole, RV FS = right ventricular fractional shortening, TV TDI S´ = Peak velocity of systolic lateral tricuspid annular motion

Tables and figures

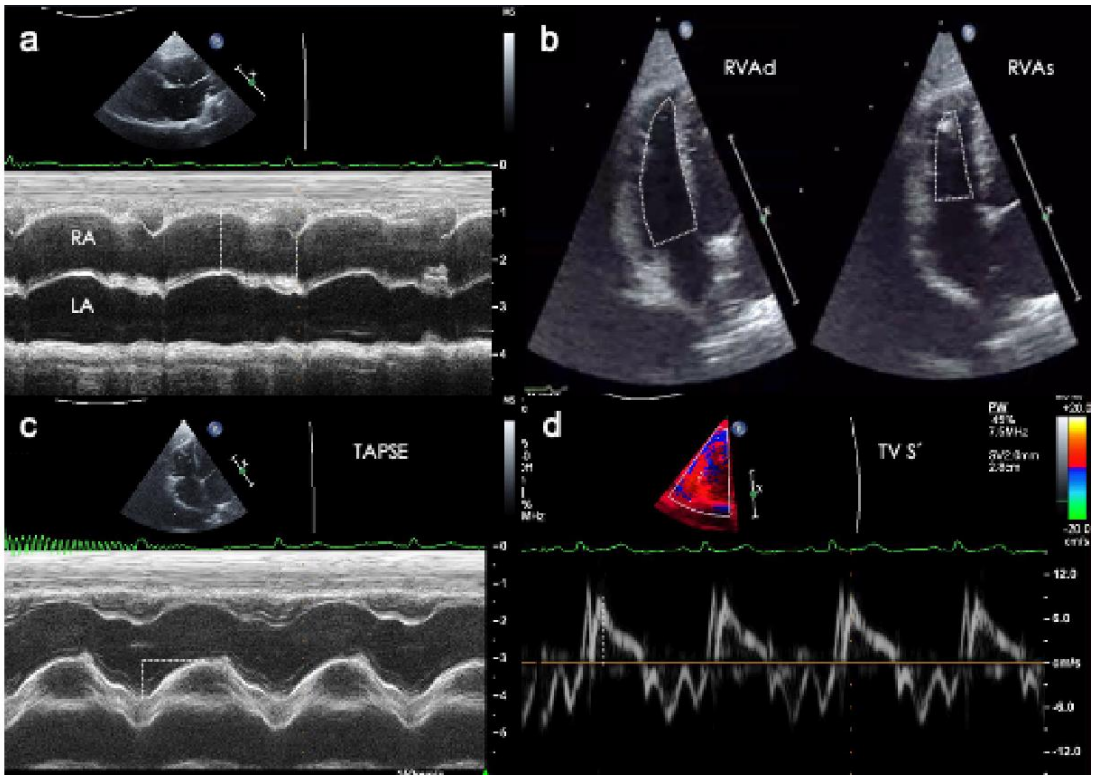

Figure 1

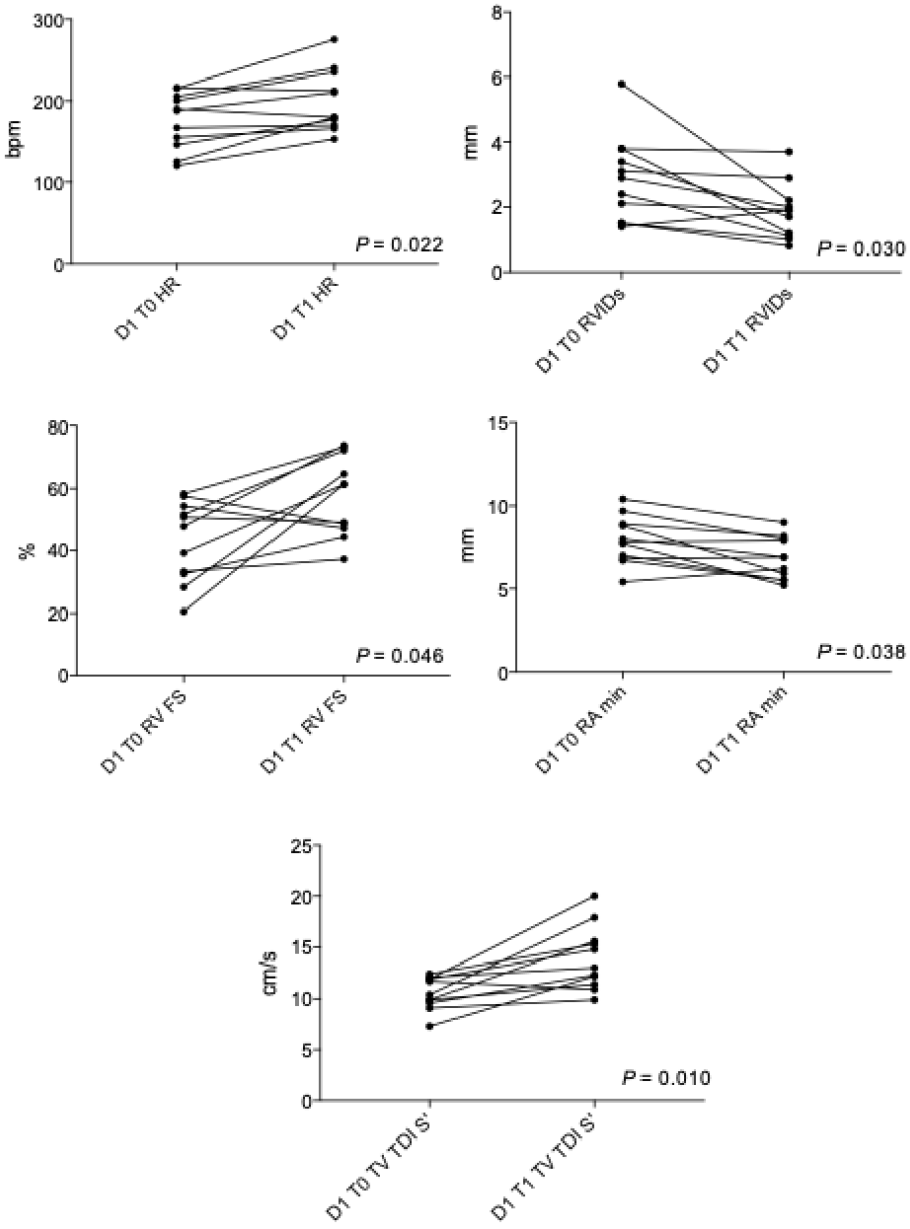
bpm
300
200
100
0
P = 0.022
D1 T0 HR
D1 T1 HR
mm
8
6
4
2
0
P = 0.030
D1 T0 RVIDs
D1 T1 RVIDs
%
80
60
40
20
0
P = 0.046
D1 T0 RV FS
D1 T1 RV FS
mm
15
10
5
0
P = 0.038
D1 T0 RA min
D1 T1 RA min
cm/s
25
20
15
10
5
0
P = 0.010
D1 T0 TV TDI S'
D1 T1 TV TDI S'

Figure 2

Table 1. Echocardiographic variables obtained in 11 healthy cats at two different time points without (DAY 0) and with (DAY 1) administering one single dose of pimobendan

	DAY 0		**DAY 1**		
Variable	**Time 0**	**Time 1h**	**Time 0**	**Time 1h (Pimobendan)**	**overall *P* value**
Heart rate (bpm)	**176.5 ± 28.3**	**173.3 ± 30.1**	**175.2 ± 34.7**	**199.8 ± 37.8*,##,§**	**<0.001**
RVIDd (mm)	5.2 ± 1.2	5.0 ± 1.2	4.9 ± 1.3	4.3 ± 1.0	0.115
RVIDs (mm)	**2.6 (2.1-2.9)**	**2.6 (2.1-3.5)**	**2.9 (1.5-3.8)**	**1.9 (1.1-2.2)#,§**	**0.018**
RV FS (%)	**47.0 ± 10.5**	**46.1 ± 12.0**	**43.1 ± 13.0**	**57.6 ± 12.8#,§**	**0.018**
RVFWd (mm)	2.5 ± 0.5	2.5 ± 0.3	2.4 ± 0.3	2.5 ± 0.2	0.910
RVAd (cm2)	1.2 (1.1-1.6)	1.5 (1.4-1.8)	1.4 (1.2-1.7)	1.4 (1.2-1.7)	0.132
RVAs (cm2)	0.5 ± 0.2	0.6 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.085
RV FAC (%)	54.5 (52.9-72.7)	63.2 (50.0-69.2)	66.7 (55.0-73.3)	68.8 (53.9-71.4)	0.058
RA_{max} (mm)	**11.4 ± 1.1**	**10.9 ± 1.3**	**10.8 ± 1.2**	**10.1 ± 1.1***	**0.042**
RA_{min} (mm)	**8.6 ± 1.5**	**7.9 ± 1.4**	**7.9 ± 1.5**	**6.8 ± 1.3**,§**	**0.007**
RA FS (%)	25.0 ± 9.5	27.6 ± 8.1	27.0 ± 9.0	32.4 ± 9.9	0.102
TAPSE (mm)	8.4 ± 1.2	9.5 ± 1.3	9.1 ± 1.7	9.1 ± 1.7	0.248
TV S'	**11.4 (8.9-12.3)**	**10.4 (8.6-11.3)**	**10.4 (9.6-11.9)**	**13 (11.4-15.6)#,§**	**0.006**

Data are expressed as mean ± standard deviation or median (interquartile range).

* = $P < 0.05$ compared to DAY 0 Time 0
** = $P < 0.01$ compared to DAY 0 Time 0
\# = $P < 0.05$ compared to DAY 0 Time 1h
= $P < 0.01$ compared to DAY 0 Time 1h
§ = $P < 0.05$ compared to DAY 1 Time 0
RA_{max} and RA_{min} = right atrial maximal and minimal internal diameter, respectively; RA FS = right atrial fractional shortening; RVAd and RVAs = right ventricular area in diastole and systole, respectively; RV FAC = right ventricular fractional area change; RV FS = right ventricular fractional shortening; RVFWd = right ventricular free wall thickness in diastole; RVIDd and RVIDs = right ventricular internal diameter in diastole and systole, respectively; TAPSE = tricuspid annular plane systolic excursion; TV S´ = peak velocity of systolic lateral tricuspid annular motion

Table 2. Within-day and between-day CV of right ventricular and atrial echocardiographic variables in 11 healthy cats and their percentage change after a single dose of pimobendan.

Variable	Within-day CV (%)	Between-day CV (%)	% change after Pimobendan (range)*	Number of cats**
Heart rate (bpm)	6.6	9	**15.3 (-5.3 to 44)**	11
RVIDd (mm)	17.1	19.8	-10.9 (-35.8 to 16.1)	4
RVIDs (mm)	18.9	22.7	**-29.9 (-68.4 to 35.7)**	8
RV FS (%)	14.7	22.8	**47.3 (-15-5 to 198.8)**	8
RVFWd (mm)	7.5	9.3	4.2 (-14.3 to 21.7)	9
RVAd (cm2)	19.3	11.9	2.7 (-35 to 33.3)	6
RVAs (cm2)	21.9	27.3	-3.5 (-50 to 25)	5
RV FAC (%)	13.7	11.7	0.3 (-23.1 to 12.5)	1
RA_{max} (mm)	8.5	8.8	-6.2 (-23.5 to 7.5)	4
RA_{min} (mm)	8.1	9.4	**-12.7 (-33 to 14.8)**	8
RA FS (%)	18.8	25.6	**30.3 (-43.3 to 107.9)**	10
TAPSE (mm)	10.4	11.7	1.8 (-23.5 to 29.7)	8
TV S'	9.4	17.4	**33.2 (-6.8 to 72.1)**	8

*percentage change of the value for each variable after pimobendan administration. **number of cats in which the percentage change after pimobendan administration exceeded the within-day CV. Percentage changes that exceed the within-day CV are shown in bold.

CV = coefficient of variation; RVIDd and RVIDs = right ventricular internal diameter in diastole and systole, respectively; RV FS = right ventricular fractional shortening; RVFWd = right ventricular free wall thickness in diastole; RVAd and RVAs = right ventricular area in diastole and systole, respectively; RV FAC = right ventricular fractional area change; RA_{max} and RA_{min} = right atrial maximum and minimum diameter, respectively; RA FS = right atrial fractional shortening; TAPSE = tricuspid annular plane systolic excursion; TV S´ = peak velocity of systolic lateral tricuspid annular motion

Acknowledgements

I would like to thank very much Dr. Marco Baron Toaldo for the mentoring and guidance during this project as well as Prof. Dr. Tony Glaus for his support and inputs. I learned a lot and I am grateful for the opportunity to study this interesting clinical field during the past year.

I would further like to thank my family and friends for all the support on my way through pre- and postgraduate studies.

Finally, many thanks belong to Kaspar Rohner and the “Tierärztliche Verrechnungsstelle GST AG” for their financial support to this dissertation.

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